Investigating suPAR as a Biomarker for Chronic Kidney Disease Stage Progression and the Survival Outcomes of Patients

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Background

- Chronic Kidney Disease (CKD) is the gradual decline in kidney function consisting of five stages that lead to kidney failure.
- The Centers for Disease Control and Prevention reported that roughly 15% of US adults (approx. 30 million) have CKD with diabetes and hypertension as primary risk factors, and those with CKD are at risk for cardiovascular disease.
- Kidney function is measured by glomerular filtration rate (GFR). GFR < 60 indicates that the patient has clinical CKD.
- There is evidence for higher levels of suPAR (soluble urokinase-type plasminogen activator receptor) being associated with 1) GFR levels, 2) change in GFR over time, and 3) developing CKD.
- Moreover, people with higher levels of suPAR experienced a greater decrease in GFR levels and a greater incidence of CKD.
- Proteinuria is a clinical biomarker for CKD stage progression.
- suPAR is a predictor for major adverse cardiovascular events.

Research Aims

1. Examine whether suPAR levels are associated with CKD stage progression for those without clinical CKD at baseline.
2. Compare the survival between (1) those with and without CKD, (2) females and males with CKD, (3) blacks and non-blacks with CKD
3. Determine the risk for experiencing a major adverse cardiovascular event (MACE) for those with CKD.

A subset of data ($n = 366$; 130 patients with clinical CKD) was sourced from the Emory Cardiovascular Biobank.

1. suPAR and CKD Stage Progression

Table 1 | Clinical multiple logistic regression model (AIC: 272.6)
n = 216 patients without clinical CKD

	Odds Ratio (95% CI)	p-value
suPAR (1000 pg/mL)	1.341 (1.043,1.738)	0.023
Age	0.988 (0.96,1.018)	0.431
Sex	0.716 (0.35,1.475)	0.361
Race (Black, non-Black)	0.636 (0.257,1.487)	0.309
BMI	1.001 (0.944,1.061)	0.976
Proteinuria	2.51 (0.52,12.372)	0.242
C-Reactive Protein	1.021 (0.977,1.067)	0.336
acearb	0.942 (0.444,2.033)	0.878
Diabetes	0.813 (0.404,1.6)	0.554
Hypertension	2.175 (0.997,5.018)	0.058
Dyslipidemia	1.105 (0.529,2.355)	0.793
Coronary Artery Disease	1.16 (0.513,2.672)	0.723
Ever Smoked	1.004 (0.514,1.975)	0.99
History of Myocardial Infarction	0.893 (0.401,1.939)	0.778

2. CKD/Risk Factor Survival

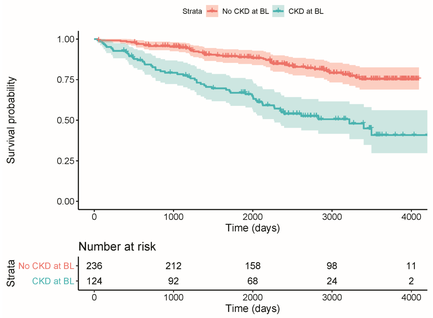

Figure 1 | Kaplan-Meier survival curves for those with and without clinical CKD at baseline. The probability of survival is higher for patients with CKD than patients without CKD ($p < 0.0001$).

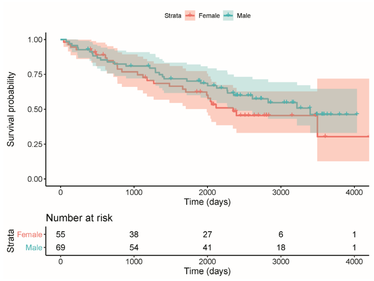

Figure 2 | Kaplan-Meier survival curves by sex for those with clinical CKD at baseline. There is not evidence to suggest a difference in the probability of survival between males and females at any time ($p = 0.2$).

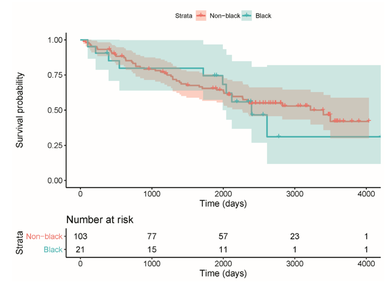

Figure 3 | Kaplan-Meier survival curves by race for those with clinical CKD at baseline. There is not evidence to suggest a difference in the probability of survival at any time ($p = 0.6$).

3. Risk of MACE

Table 2 | Clinical Cox PH regression model (AIC: 596.81)
n = 111 patients with clinical CKD

	Hazard Ratio (95% CI)	p-value
suPAR (1000pg/mL)	1.232 (1.03,1.473)	0.022
Age	1.016 (0.99,1.043)	0.224
Sex	0.857 (0.507,1.448)	0.564
Race	0.611 (0.277,1.348)	0.222
BMI	0.977 (0.931,1.026)	0.348
C-Reactive Protein	1.009 (0.992,1.026)	0.315
acearb	1.287 (0.671,2.468)	0.448
Diabetes	0.782 (0.422,1.448)	0.434
Hypertension	0.848 (0.433,1.663)	0.632
Dyslipidemia	0.609 (0.326,1.136)	0.119
CAD	1.289 (0.69,2.408)	0.426
Ever Smoked	0.861 (0.514,1.44)	0.568
History of Myocardial Infarction	0.746 (0.413,1.347)	0.331
Moderate CKD at Baseline	0.904 (0.478,1.711)	0.757

Model Selection

Two types of models built for research aims 1 and 3 :

1. Clinical model: predictors selected based on literature review and clinical significance
2. Stepwise selected model: final model chosen based on AIC

(Univariate tests were also conducted where suPAR was the only significant predictor at 0.05; creatinine was also considered.)

Table 3 | Aim 1 stepwise model: suPAR and CKD stage progression (AIC: 252.55)

	Odds Ratio (95% CI)	p-value
suPAR (1000pg/mL)	1.332 (1.054,1.702)	0.018
HTN	1.884 (0.93,4.053)	0.089
Creatinine	0.221 (0.038,1.19)	0.084

Table 4 | Aim 3 stepwise model: risk of MACE (AIC: 582.79)

	Hazard Ratio (95% CI)	p-value
suPAR (1000pg/mL)	1.198 (1.067, 1.345)	0.002
Age	1.021 (0.996, 1.047)	0.094
Dyslipidemia	0.633 (0.372, 1.078)	0.092

Conclusions

- Aim 1: suPAR levels are significantly associated with CKD stage progression for those without clinical CKD. Specifically, the odds for having progressed to a later stage of CKD is 34% higher for each increase in 1,000 pg/mL of suPAR.
- Aim 2: The probability of survival is significantly higher for those without clinical CKD compared to those with CKD. While males and non-blacks had a higher probability of survival, these results were not statistically significant.
- Aim 3: suPAR level was the only statistically significant risk factor for MACE. While the stepwise selection method produced models that had fewer predictors than the clinical models, suPAR was still the only significant predictor at the 0.05 level.

Future work: Incorporate interaction terms and identify which predictors may be moderators or mediators (in conjunction with suPAR) for CKD stage progression and/or MACE

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